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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

June 15, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Critical Path Initiative [Docket No. 2004-N-0181, 69 Federal Register, 21839 (April 22, 2004)]

Dear Madam/Sir:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA shares Food and Drug Administration's (FDA's) concern, expressed in the *Critical Path* report, over the numbers of new drugs approved in recent years and welcomes the Agency's initiative to join with its stakeholders to think creatively about translational research and its potential impact on pharmaceutical development and the regulatory review process. We appreciate that the report concretely advances FDA's mission to promote medical innovation that former Commissioner McClellan articulated so well in January 2003. The report makes some proposals of translational research opportunities for collaborative evaluation and implementation – we have provided our initial response to these, and also listed some opportunities that we believe would merit examination but were not mentioned in the report.

We see the opportunities being organized under the following headings:

1. Application of new technologies and technical approaches
2. Evolution of regulatory processes
3. Resources and efficiency

1. <u>Application of new technologies and technical approaches</u>
   a) Data mining
   FDA proposes several development areas and operations that might benefit from analysis of data mined from FDA product review datasets. Results from this work could potentially illuminate trends or validate hypotheses. Specifically

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highlighted are possible applications in development failure analysis, validation of in vitro and in vivo animal model tests, and testing pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of drugs in special populations such as pediatrics. Given that the potential application set would, in aggregate, require a major investment of resources, an effort to determine the feasibility of FDA data mining may be an appropriate first step. A so-tasked FDA-industry-academic work group could consider the conceptual pros and cons, validation issues, data quality standards, potential legal issues, and the range of workable applications. Specific data mining demonstration projects could follow, to test these structures and processes, and to provide a basis of experience to adjust the models.

b) Biomarkers

The need to expand the understanding and use of both safety and efficacy biomarkers in drug development is supported in the *Critical Path* report. FDA proposes, "*. . .for biomarkers that currently appear promising, specific projects be undertaken to assemble existing data on the association of the marker with clinical outcomes, assemble existing performance data with respect to current outcomes, identify the degree of uncertainty, identify studies needed to answer remaining questions to reduce uncertainty.*" It is assumed that FDA means *biomarkers that currently appear promising for regulatory decision-making*, rather than all biomarkers that might be used in drug development – an important distinction. This is likely an area where FDA and industry objectives are closely aligned and well-suited to collaborative research and development. Advancing the *Critical Path* proposal even to the point of agreeing among stakeholders on a list of "promising biomarkers," would be important progress, particularly if industry, FDA, and the National Institutes of Health (NIH) were all involved. FDA has indicated the intent to outline a process for the regulatory acceptance of new genomic biomarkers in the final guidance on Pharmacogenomic Data Submissions, due in June 2004. This process might serve as a model for the acceptance of other types of markers. Marker validation studies would be facilitated if this process were in place.

An important practical consideration in the validation of biomarkers is the accumulation of sufficient data, preferably from multiple sources, to demonstrate a persuasive statistical or evidentiary case. In principle, PhRMA would be interested to explore creative ways to do this, for example:

i) With appropriate incentives and safeguards for data confidentiality, groups of sponsors might consider *pooling experimental data* for analysis by a third party, who could then prepare a case for presentation to the Agency. This is a precedented model, having been used in the validation of RNA copy number as a surrogate endpoint for the efficacy of drugs to treat AIDS/HIV.

ii) Similarly, it may be appropriate for cross-institutional, multidisciplinary work groups to be established to study the design and validation of *compound biomarkers made up of multiple simultaneous or correlated biological events or findings*. This approach would be

particularly appropriate in situations where the availability of such a biomarker would be an important aid to drug development and where there is a reasonable chance of a favorable validation outcome. FDA could be an important facilitator in this biomarker validation process.

c) Imaging
Advancing the use of new imaging technologies in drug development is also highlighted by FDA as a *Critical Path* objective. Approval of novel imaging technologies could involve more than one Agency Center and so, consideration of methods to coordinate reviews across Centers should be a component of this project, with a goal to develop industry guidance. Analogous goals and processes might also apply to the *Critical Path* call for improved predictive software for device changes.

d) Product Manufacturing
Incorporating the most up-to-date science into manufacturing regulation to enable and encourage manufacturing innovation is recognized as a priority. Current joint FDA-industry efforts to advance risk-based manufacturing regulations should continue to be aggressively pursued.

e) Prevention therapies
Encouraging the development of medicines for use in *primary prevention* of disease is an important public health objective. A joint industry-FDA task force to explore opportunities to facilitate this work should be considered. This group could both recommend policies to accelerate the development of new prevention-oriented drugs and also suggest means to harmonize review Center practices specific to prevention therapies. Parameters to define an accelerated contingent review process for disease prevention drug candidates, based on biomarker data, could be considered as well.

2. Evolution of regulatory processes
   a) Optimizing Phase 3 – Phase 4 benefit/risk assessment efficiency
   Systematic assessment, by therapeutic area or drug class, as to the scope of safety and efficacy evidence needed by regulators at the time of application submission versus that which could appropriately be provided post-approval, is needed. Further, a process for ongoing review by therapeutic area to distinguish necessary Phase 4 studies from those that are informative but not required for the safe use of a drug should be considered. Absent this process, sponsors can be faced with escalating Phase 4 programs with little or no offsetting reduction in the Phase 3 testing requirements.

   b) Integration of diagnostics regulation with drug approval
   Drugs with companion diagnostics to treat targeted patient populations will become increasingly common, and this in turn should lead to significant improvements in efficacy and/or safety. A smooth and well-understood regulatory pathway for approval of drug-diagnostic combinations is needed.

PhRMA appreciates the opportunity to cosponsor the planned joint FDA – industry workshop on 29th July to discuss this issue.

c) Multiple efficacy endpoints
New drug approval in certain therapeutic areas including migraine, sleep disorders, fibromyalgia, antibiotics, and Alzheimer's disease, increasingly requires statistically significant efficacy demonstration for more than one endpoint. As added endpoint requirements can lead to increased study sample sizes, a joint industry-FDA analysis by therapeutic area, of the prevalence of multiple endpoint requirements could be valuable in efforts to optimize development efficiency. With these data, critical review of endpoint requirement norms may reveal opportunities to streamline clinical trial requirements. This process would be complementary to that described above at 1.b) ii and below at 2.d).

d) Consensus on clinical endpoints
There is a pressing need for consensus both nationally and globally among regulators, physicians, and innovators as to appropriate clinical trial outcomes measures. Selecting a forum for stakeholders to discuss and agree on priorities, methods, sponsors, and conclusions is a necessary first step. The ICH process is a potential candidate for this forum since many procedures and relationships are already in place, but other multilateral agreement forums could also be structured. Means to facilitate incorporation of clinical outcome information, especially quality of life and health economics measures, into product labeling should be considered in this process. Particular attention should go to maintaining consistency between FDA review division and Division of Drug Marketing, Advertising and Communications (DDMAC) product promotion policies to encourage development of new drugs and exploration of new indications.

e) International regulatory harmonization
While the need for global consensus on outcomes measures is noted in the *Critical Path* paper, regulatory harmonization is a broader objective. Drug development is an international endeavor and harmonization of regulatory requirements to best practices, where feasible, will have a favorable effect on drug development efficiency. Conversely, the benefits of FDA initiatives to develop new tools for regulatory review and approval will be significantly compromised if sponsors find that other major authorities continue to operate on "yesterday's models." We see this as having a broader scope than the consensus on efficacy endpoints discussed at 2(c).

3. Resources and efficiency
a) The NIH "Strategic Roadmap"
This document, published in 2003, is acknowledged in the FDA *Critical Path* paper, and the potential value of NIH collaboration in certain areas is suggested. Model-based drug development and targeted proteomics and toxicogenomics research are potential areas of cooperative investigation (in addition to biomarker

research) where NIH resources and expertise could complement potential FDA and industry efforts. Again a framework for collaboration is needed.

b) Informatics and information technology standardization and innovation
FDA and industry should move, where possible, to common technology platforms and standards for information exchange. This may require significant investment, but PhRMA believes that these improvements will generate significant positive returns.

c) Funding and staffing for FDA's *Critical Path* project work
Critical Path initiatives will undoubtedly yield efficiencies; however this work should not distract FDA staff from their core mission to review new products. Regulatory efficiency, Quality Systems, and GMP initiative goals should not be compromised in pursuit of *Critical Path* objectives, nor should staff and reviewer training programs. At the same time, it is vital that *Critical Path* projects be resourced adequately to support important project objectives.

Progress toward the stated *Critical Path* objectives will require participation from various stakeholders including industry and NIH. There will be a need for each of the contributors to understand the interests and accommodate the constraints of other parties. Leveraging unique FDA perspectives and experience may well have great benefits for drug development through the facilitated application of new techniques and more efficient, consistent, and predictable regulation. PhRMA applauds the innovative thinking behind the *Critical Path* initiative and looks forward to a productive partnership with FDA to realize these concepts.

Sincerely,

Alice E. Till, Ph.D.

CC N. Myers
J. Woodcock